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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,755	09/10/2003	Richard A. Dixon	NBLE:007US	4103

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EXAMINER
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KALLIS, RUSSELL

ART UNIT	PAPER NUMBER
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1638

MAIL DATE	DELIVERY MODE
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04/21/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/659,755

**Applicant(s)**

DIXON ET AL.

**Examiner**

RUSSELL KALLIS

**Art Unit**

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 30 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☐ Claim(s) 2-35 and 46-50 is/are pending in the application.
- 4a) Of the above claim(s) 36-45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-35 and 46-50 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 1/08/4/08
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

Claims 2-50 are pending. Claim 1 is cancelled. Claims 36-45 are withdrawn. Claims 2-35 and 46-50 are examined.

Rejection of Claim 2 under 35 U.S.C. 102(b) as being anticipated is withdrawn in view of Applicants' amendments.

#### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2-35 and 46-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu O. *et al.* Plant Physiology, 2000; Vol. 124, pp. 781-793 in view of Wisman *et al.* PNAS, Oct. 1998, Vol. 95, pp. 12432-12437 and in further view of Applicant's disclosure of the state of the prior art.

The claims are broadly drawn to a method of increasing isoflavonoid biosynthesis in a plant by down regulating flavanone 3-hydroxylase and upregulating expression of isoflavone synthase and chalcone isomerase and plants transformed thereby.

Yu teaches production of genistein (i.e. an isoflavonoid) in a non-legume dicot and monocot plant and plant transformed with isoflavone synthase (see abstract and page 2000 col. 2 1<sup>st</sup> full paragraph; and page 783 col. 1 1<sup>st</sup> paragraph); upregulating the phenylpropanoid pathway

to increase genistein production in the presence of isoflavonoid synthase relative to a non-upregulated control (page 785 column 1 last paragraph and page 785 column 2; and Table II on page 786); that the heterologous isoflavone synthase competes with the endogenous enzyme (flavanoid 3-hydroxylase) for naringenin in the phenylpropanoid pathway (page 785 from column 1 last paragraph to col. 2 end of section); and that in legumes the production of isoflavonoids are environmentally influenced and those levels may be enhanced by introduction of the isoflavone transgene (page 782 from col. 1 line 31 to col. 2 line 9); and that further engineering to more specifically increase the level of IFS substrate, reduce activities of competing endogenous pathways may allow higher levels of isoflavone accumulation in plants (page 789 under Prospects for Isoflavone Metabolic Engineering).

Yu does not teach down regulating flavanone 3-hydroxylase.

Wisman teaches a *tt6* mutant in *Arabidopsis* wherein the *tt6* gene comprises a mutant flavanone 3-hydroxylase that has lost its' function of converting its' substrate into product thereby allowing for the accumulation of naringenin (i.e. the substrate of the flavanone 3-hydroxylase) (see page 12,435 in figure 3 part A and B).

Applicant's disclosure teaches that the instantly claimed sequences were taught in the art (see specification pages 14-15 flavanone 3-hydroxylase SEQ ID NO: 10, 13, 15; page 45 chalcone isomerase SEQ ID NO: 3; page 43 for isoflavone synthase i.e. SEQ ID NO: 1; and McKhann and Hirsh, 1994 from Applicant's IDS for SEQ ID NO: 5 and 6).

It would have been obvious at the time of filing for one of ordinary skill in the art to increase isoflavone synthase expression in any plant to increase isoflavonoid biosynthesis. One of ordinary skill would have been motivated by the success of Yu in both achieving the synthesis

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of the isoflavone genistein by transforming *Arabidopsis*, maize and tobacco with isoflavone synthase and in further up-regulating expression of the genes in the phenylpropanoid pathway to further increase the levels of genistein in maize cells expressing isoflavone synthase successfully. One of ordinary skill in the art would have appreciated that transformation with individual genes encoding chalcone synthase and chalcone isomerase could substitute for upregulating the phenylpropanoid pathway taught by Yu, and that the steps leading to the synthesis of naringenin the substrate for isoflavone synthase were well described in the art and the genes readily available, and would have been further motivated by the teachings of Yu and that eliminating or reducing flavanone 3-hydroxylase expression would reduce or eliminate competition for naringenin between flavanone 3-hydroxylase and isoflavone synthase, and by the teachings of Wisman that eliminating or reducing flavanone 3-hydroxylase activity would allow for naringenin accumulation; and that one of ordinary skill would have a reasonable expectation of success in both producing an isoflavonoid in plant by transformation with isoflavonoid synthase and decreasing competition for naringenin by endogenous enzymes such as flavanone 3-hydroxylase; wherein reducing or down-regulating flavanone 3-hydroxylase expression is an obvious optimization of genistein or isoflavonoid production in a plant because down regulating flavanone 3-hydroxylase expression in a plant will not alone increase isoflavonoid production but rather eliminate competition as taught by Yu; and wherein transforming a legume such as alfalfa is obvious given the success of Yu in transforming non-legumes and producing an isoflavonoid and the teachings of Yu that in legumes the production of isoflavonoids are environmentally influenced and those levels may be enhanced by introduction of the isoflavone transgene.

***Claim Rejections - 35 USC § 103***

Claims 2-35 and 46-50 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 7,189,895 (McGonigle, B. and Odell, J.) with the effective filing date of June 13, 2002 (60/388,280) in view WO 00/44909 of published August 3<sup>rd</sup>, 2000; and in further view of Applicant's disclosure of the state of the prior art. This rejection is maintained for the reasons of record set forth in the Official action mailed 7/30/2007. Applicant's arguments filed 1/30/2008 have been considered but are not deemed persuasive.

The claims are broadly drawn to a method of increasing isoflavonoid biosynthesis in a plant by down regulating flavanone 3-hydroxylase and upregulating expression of isoflavone synthase and chalcone isomerase and synthase and plants transformed thereby.

Patent 7,189,895 teaches a method of increasing isoflavonoid biosynthesis in a isoflavonoid producing plant by down regulating flavanone 3-hydroxylase expression by transformation with an antisense flavanone 3-hydroxylase and up-regulating expression of isoflavone synthase and chalcone isomerase by transformation with maize C1 and R transcription factors in conjunction and plants transformed thereby (see columns 25-26; and claims 1-10); and that the C1 and R transcription factors upregulate expression of chalcone synthase and chalcone isomerase as well as the expression of other enzymes of the phenylpropanoid pathway in plants (see column 3 lines 1-23); that flavaone 3-hydroxylase and isoflavone synthase compete for substrate (col. 2 lines 15-29)

WO 00/44909 teaches a method of increasing isoflavonoid biosynthesis in a plant by transformation with an isoflavone synthase (see Examples 10-17 p. 45-57).

Applicant's disclosure teaches that the instantly claimed sequences were taught in the art (see specification pages 14-15 flavanone 3-hydroxylase SEQ ID NO: 10, 13, 15; page 45 chalcone isomerase SEQ ID NO: 3; page 43 for isoflavone synthase i.e. SEQ ID NO: 1; and McKhann and Hirsh, 1994 from Applicant's IDS for SEQ ID NO: 5 and 6).

It would have been obvious at the time of filing for one of ordinary skill in the art to increase isoflavone synthase in any plant by down regulating flavanone 3-hydroxylase and up-regulating expression of isoflavone synthase and chalcone isomerase by substituting specific genes encoding chalcone synthase and chalcone isomerase for the transcription factors C1 and R that up-regulate the phenylpropanoid pathway. One would have been motivated by the teachings of U.S. Patent 7,189,895 and WO 00/44909 that chalcone synthase and chalcone isomerase are the penultimate and last steps leading to the synthesis of naringenin the substrate for isoflavone synthase and could reproduce the upregulation of the pathway achieved by using the transcription factors C1 and R by transformation with polynucleotides encoding chalcone synthase and chalcone isomerase; and that inhibiting flavanone 3-hydroxylase would reduce or eliminate competition between flavanone 3-hydroxylase and isoflavone synthase for naringenin (see col. 2 lines 15-39 and figure 1) and result in higher levels of isoflavonoids in plants transformed therewith and with isoflavone synthase (see column 24-25); and had a reasonable expectation of given the success of patent 7,189,895 and patent WO 00/44909.

Applicants' assertion that the '895 Patent and WO/44909 can not be used as prior art against the instant claims is premature and improper because the condition for an interference exists. Applicant is urged to file under 41.202 CFR to overcome the prior art.

Further Applicants' request for examination of withdrawn claims 36-44 is improper because Applicants' assertion that claims 24 and 40 are allowable is premature and the withdrawn claims are drawn to different subject matter as stated in the previous restriction of 9/07/2006. Moreover, Applicant has cancelled the linking claim.

**§ 41.202 Suggesting an interference.**

- (a) *Applicant*. An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must:
- (1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference,
  - (2) Identify all claims the applicant believes interfere, propose one or more counts, and show how the claims correspond to one or more counts,
  - (3) For each count, provide a claim chart comparing at least one claim of each party corresponding to the count and show why the claims interfere within the meaning of § 41.203(a),
  - (4) Explain in detail why the applicant will prevail on priority,
  - (5) If a claim has been added or amended to provoke an interference, provide a claim chart showing the written description for each claim in the applicant's specification, and
  - (6) For each constructive reduction to practice for which the applicant wishes to be accorded benefit, provide a chart showing where the disclosure provides a constructive reduction to practice within the scope of the interfering subject matter.



***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Russell Kallis/  
Primary Examiner, Art Unit 1638  
April 14, 2008